## REMARKS

Claims 6, 10-16, and 20 have been canceled without prejudice. Claims 1-3 and 7 have been amended to improve the clarity of the claim and more particularly point out certain characteristics of the antibody. Support for Applicants' amendments and new claims can be found throughout the specification (e.g., page 7, lines 21-23; page 8, lines 1-3; page 10, lines 11-20; page 11, lines 3-12; page 20, lines 6-11; and Figures 10-11) and original claims (e.g., claims 2-3). No new matter has been introduced and no new issue has been raised. The amendments have been made solely to expedite allowance. Applicants reserve the right to pursue claims of similar or differing scope in future applications.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Information Disclosure Statement

Applicants note that the Examiner has considered and initialed the Information Disclosure Statements filed on June 16, 2006.

However, the Examiner did not consider three references (cite Nos.: CB, CC, and CD) because they had incomplete citations. Applicants point out that these three references were clearly identified with their corresponding GenBank Accession Numbers. Nonetheless, Applicants hereby resubmit copies of these three references together with their full citations on the SB/08 Form. Applicants respectfully request the Examiner to consider these references.

Election/Restriction

The Examiner has acknowledged Applicants' election, with traverse, of Group I (claims 1-3, 7-9, and 20) as well as the election of the antibody consisting of a heavy chain of SEQ ID NO: 17 and a light chain of SEQ ID NO: 20 in the Response filed on October 28, 2008. The Examiner has withdrawn claims 4-6 and 10-19 from further consideration as being drawn to nonelected inventions.

Double Patenting

Claims 1, 7, and 20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 9, 10, and 15 of the copending Application No: 10/966,406.

Applicants note that these two copending applications were filed by different inventive entities having two common inventors (Francis J. Carr and Anita A. Hamilton). Applicants point out that the copending Application No: 10/966,406 was abandoned as evidenced by the Notice of Abandonment issued on February 11, 2009, thereby rendering the rejection moot.

Claim Objections

Claim 20 is objected to because it depends from a nonelected invention. In response, Applicants have canceled claim 20 without prejudice, rendering the objection moot.

Claim Rejections under 35 USC § 112, First Paragraph

Claims 1-3, 7-9, and 20 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

Specifically, the Examiner asserts that "[t]he specification is not enabling for the claimed antibodies, wherein they are 'de immunized' as per the definition of said term in the specification. The specification has not provided actual evidence that the claimed antibodies are 'de immunized' and the state of art is such that is unpredictable in the absence of appropriate evidence as to whether the claimed antibodies are in fact 'deimmunized' as per the definition of said term in the specification." See Office Action, page 3, lines 24-29.

Applicants respectfully disagree. Nonetheless, solely to expedite prosecution of the application, Applicants have amended independent claim 1 to recite "a de-immunized anti-CD3 antibody, wherein one or more potential T cell epitopes are altered in at least one heavy chain or at least one light chain, wherein the potential T cell epitopes in the heavy chain are selected from the group consisting of residues 5, 11, 12-13, 20, 29, 38, 40, 61-68, 70, 81, 83-84, 87-88, 91, and 115 of SEQ ID NO: 10, and wherein the potential T cell epitopes in the light chain are selected from the group consisting of residues 10-11, 13, 18-19, 21, 29, 39, 41-42, 59-60, 62, 69, 75-77, 99, 103, and 106 of SEQ ID NO: 18." Applicants have also added new claims 21-27 which are directed to de-immunized anti-CD3 antibodies having specific sequences, and added new claims 28-29 which are directed to de-immunized anti-CD3 antibody heavy or light chain variable region having specific sequences. Support for the claim amendments can be found throughout the specification (e.g., page 7, lines 21-23; page 8, lines 1-3; page 10, lines 11-20; page 11, lines 3-12; page 20, lines 6-11; and Figures 10-11) and original claims (e.g., claims 2-3). Applicants contend that the structural and functional limitations listed in amended independent claims 1, 21, and 28-29 adequately describe

the claimed subject matter, and allow one of skill in the art to envision the antibodies or the antibody variable regions.

Applicants submit that the specification is enabling for the full scope of the claims as amended. The specification teaches a number of de-immunized anti-CD3 antibodies, including de-immunized heavy chain variable regions (SEQ ID NOs: 11-17) and de-immunized light chain variable regions (SEQ ID NOs: 19-20) (see, e.g., page 20, lines 6-11; and Figures 10-11). In addition, the specification provides detailed descriptions on how to identify potential T cell epitopes within an antibody sequence and how to make the de-immunized anti-CD3 antibodies as claimed (e.g., page 10, line 1 – page 12, line 1; and the Examples on pages 17-29). In view of the teachings in the specification and the knowledge in the art at the time this application was filed, one of skill in the art would know how to practice the full scope of independent claims 1, 21, and 28-29, with no undue experimentation.

Furthermore, Applicants wish to draw the Examiner's attention to the facts in *In re Wands*, the often-cited case that sets forth the enablement standard. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). In *In re Wands*, the claims at issue relate to an immunoassay method for HBsAg using high-affinity monoclonal IgM antibodies. The broadest claim on appeal reads:

1. An immunoassay method utilizing an antibody to assay for a substance comprising hepatitis B-surface antigen (HBsAg) determinants which comprises the steps of:

contacting a test sample containing said substance comprising HBsAg determinants with said antibody; and

determining the presence of said substance in said sample;

wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least $10^9$ $M^{-1}$.

The PTO Board finally rejected the claims on grounds of lack of enablement. Specifically, the sole issue is whether it would require undue experimentation to make other high-affinity IgM monoclonal antibodies with the recited avidity. The CAFC reversed the PTO Board's decision, concluding that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." *Id.* at 740. Further, "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well

known." *Id.* In particular, with regard to the production of hybridomas, the CAFC declined to find Wands' 40% failure rate as evidence of undue experimentation, noting "[t]he record indicates that cell fusion is a technique that is well known to those of ordinary skill in the monoclonal antibody art, and there has been no claim that the fusion step should be more difficult or unreliable where the antigen is HBsAg than it would be for other antigens." *Id.*

In this case, the pending claims relate to de-immunized anti-CD3 antibodies or the variable regions of such antibodies. The specification teaches that "[i]n the method which has been termed 'de-immunization' and is described herein, amino acids within the antibody sequence that are predicted to bind effectively to HLA molecules are changed such that they no longer bind HLA and thus can no longer stimulate a T cell response" (page 5, lines 11-15). Also, the specification teaches that "[t]he anti-CD3 antibody is de-immunized. De-immunization renders the anti-CD3 antibody non-immunogenic, or less immunogenic, to a given species. De-immunization can be achieved through structural alterations to the anti-CD3 antibody" (page 10, lines 1-3). Thus, the claimed de-immunized antibodies have a defined function which is characterized by its inability to bind HLA and thus its inability to stimulate a T cell response. As the CAFC has decided in *In re Wands*, it is merely routine experimentation (and thus enabling) for a skilled artisan to screen for antibodies with a particular function. Here, one of skill in the art only needs to screen more antibodies and verify whether the antibodies have the "de-immunization" function.

Finally, Applicants point out that, "[i]n order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (MPEP 2164.04).

In this case, the Examiner has not provided adequate reasoning to support the contention that the claims are not enabled for the recited de-immunized anti-CD3 antibodies. As described above, the specification provides examples of de-immunized anti-CD3 antibodies and teaches how to make de-immunized anti-CD3 antibodies. Further, the level of skill in the art was high at the time of the filing date of the present application. In fact, the techniques involved in the invention, all of which were well known in the art even before the filing date, are highly reliable and can be readily practiced by a skilled artisan. Applicants note that the Examiner cites Conry et al. in the enablement rejection, asserting that "Conry et al. disclose that the HAMA response to a xenogeneic antibody can occur independent of T cell epitopes on said antibody (e.g. preexisting cross reactive antibodies). Thus, the antibodies would not be 'deimmunized' when administered to patients with preexisting antibodies." See Office Action, page 5, lines 4-13. Applicants respectfully disagree. This cited reference is irrelevant and does not support the enablement rejection. As described above, the de-immunized antibodies or the variable regions of the de-immunized antibodies of independent claims 1, 21, and 28-29 have a function which is characterized by the inability to bind HLA and thus the inability to stimulate a T cell response. The possibility of preexisting cross reactive antibodies, which is disclosed by Conry et al., simply does not affect the function of the recited de-immunized antibodies. The Examiner has not provided any reasoned basis on which to doubt that the instantly claimed de-immunized antibodies or their variable regions would be operative, thereby failing to meet the burden of establishing a *prima facie* case of lack of enablement.

In sum, Applicants' specification teaches how to carry out the claimed invention, and there is no undue experimentation necessary to practice the full scope of the invention as recited in independent claims 1, 21, and 28-29. In the absence of probative evidence to the contrary from the Examiner, the data in the instant specification favors a finding of the enablement of the claimed antibodies or their variable regions. Applicants submit that the pending claims as amended are enabled. Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection.

Claim Rejections under 35 USC § 102(e) or 102(a)

Claims 1, 7, and 20 are rejected under 35 U.S.C. § 102(e) or 102(a) as being anticipated by Bluestone et al. (US Patent No. 6,491,916). Applicants respectfully traverse this rejection.

As described above, Applicants have amended independent claim 1 to recite "a de-immunized anti-CD3 antibody, wherein one or more potential T cell epitopes are altered in at least one heavy chain or at least one light chain, wherein the potential T cell epitopes in the heavy chain are selected from the group consisting of residues 5, 11, 12-13, 20, 29, 38, 40, 61-68, 70, 81, 83-84, 87-88, 91, and 115 of SEQ ID NO: 10, and wherein the potential T cell epitopes in the light chain are selected from the group consisting of residues 10-11, 13, 18-19, 21, 29, 39, 41-42, 59-60, 62, 69, 75-77, 99, 103, and 106 of SEQ ID NO: 18." Applicants have also added new claims 21-27 which are directed to de-immunized anti-CD3 antibodies having specific sequences, and new claims 28-29 which are directed to de-immunized anti-CD3 antibody heavy or light chain variable region having specific sequences.

The standard for anticipating a claim is clearly outlined in MPEP 2131, and this standard is further supported by the Courts. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1978).

Applicants submit that Bluestone et al. fail to satisfy the criteria for anticipating the present invention. Bluestone et al. disclose generation of humanized anti-CD3 antibodies by transferring the murine OKT3 antibody's antigen-binding site into a human antibody framework (see, e.g., the abstract; and Example 3 on columns 20-21). However, Bluestone et al. do **not** teach a de-immunized anti-CD3 antibody, wherein one or more potential T cell epitopes are altered in at least one heavy chain or at least one light chain, wherein the potential T cell epitopes in the heavy chain are selected from the group consisting of residues 5, 11, 12-13, 20, 29, 38, 40, 61-68, 70, 81, 83-84, 87-88, 91, and 115 of SEQ ID NO: 10, and wherein the potential T cell epitopes in the light chain are selected from the group consisting of residues 10-11, 13, 18-19, 21, 29, 39, 41-42, 59-60, 62, 69, 75-77, 99, 103, and 106 of SEQ ID NO: 18 (as recited in independent claim 1). Further, Bluestone et al. do **not** teach a de-immunized anti-CD3 antibody comprising a heavy chain variable region

comprising a sequence selected from the group consisting of SEQ ID NOs: 15, 16 and 17 (as recited in independent claim 21). Finally, Bluestone et al. do **not** teach a de-immunized anti-CD3 antibody heavy chain variable region comprising a sequence selected from the group consisting of SEQ ID NOs: 15, 16 and 17 (as recited in independent claim 28), or a de-immunized anti-CD3 antibody light chain variable region comprising a sequence selected from the group consisting of SEQ ID NOs: 19 and 20 (as recited in independent claim 29). Thus, Bluestone et al. fail to meet the limitations of independent claims 1, 21, or 28-29 and thus fail to anticipate the claimed subject matter.

In sum, Bluestone et al. (US Patent No. 6,491,916) fail to anticipate independent claims 1, 21, or 28-29. For the same reasons, all claims that depend from claims 1, 21, or 28-29 are not anticipated by Bluestone et al. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim Rejections under 35 USC § 102(b)

Claims 1, 7, and 20 are rejected under 35 U.S.C. § 102(b) as being anticipated by Bluestone et al. (WO 94/28027). Applicants respectfully traverse this rejection.

Like the above-cited Bluestone et al. (US Patent No. 6,491,916), this cited reference (Bluestone et al., WO 94/28027) also disclose generation of humanized anti-CD3 antibodies by transferring the murine OKT3 antibody's antigen-binding site into a human antibody framework (see, e.g., the abstract; and Example 3 on pages 39-43). However, Bluestone et al. (WO 94/28027) do **not** teach a de-immunized anti-CD3 antibody, wherein one or more potential T cell epitopes are altered in at least one heavy chain or at least one light chain, wherein the potential T cell epitopes in the heavy chain are selected from the group consisting of residues 5, 11, 12-13, 20, 29, 38, 40, 61-68, 70, 81, 83-84, 87-88, 91, and 115 of SEQ ID NO: 10, and wherein the potential T cell epitopes in the light chain are selected from the group consisting of residues 10-11, 13, 18-19, 21, 29, 39, 41-42, 59-60, 62, 69, 75-77, 99, 103, and 106 of SEQ ID NO: 18 (as recited in independent claim 1). Further, Bluestone et al. (WO 94/28027) do **not** teach a de-immunized anti-CD3 antibody comprising a heavy chain variable region comprising a sequence selected from the group consisting of SEQ ID NOs: 15, 16 and 17 (as recited in independent claim 21). Finally, Bluestone et al. (WO

94/28027) do **not** teach a de-immunized anti-CD3 antibody heavy chain variable region comprising a sequence selected from the group consisting of SEQ ID NOs: 15, 16 and 17 (as recited in independent claim 28), or a de-immunized anti-CD3 antibody light chain variable region comprising a sequence selected from the group consisting of SEQ ID NOs: 19 and 20 (as recited in independent claim 29). Thus, Bluestone et al. (WO 94/28027) fail to meet the limitations of independent claims 1, 21, or 28-29 and thus fail to anticipate the claimed subject matter.

In sum, Bluestone et al. (WO 94/28027) fail to anticipate independent claims 1, 21, or 28-29. For the same reasons, all claims that depend from claims 1, 21, or 28-29 are not anticipated by Bluestone et al. Reconsideration and withdrawal of this rejection are respectfully requested.

## CONCLUSION

In view of the above remarks, Applicants believe that the pending application is in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. **18-1945**, under Order No. **ALXN-P01-106** from which the undersigned is authorized to draw.

Dated: February 20, 2009

Respectfully submitted,

By _____

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